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(54) Title: PROCESS FOR PREPARING NITROOXYALKYL SUBSTITUTED ESTERS OF CARBOXYLIC ACIDS, INTERMEDIATES USEFUL IN SAID PROCESS AND PREPARATION THEREOF

(57) Abstract: The present invention refers to a process for preparing a compound of general formula (A), as reported in the description, wherein R is a radical of a drug and R1-R12 are hydrogen or alkyl groups, m, n, o, q, r and s are each independently an integer from 0 to 6, and p is 0 or 1, and X is O, S, SO, SO2, NR13 or PR13 or an aryl, heteroaryl group, said process comprising reacting a compound of formula (B) R-COOZ (B) wherein R is as defined above and Z is hydrogen or a cation selected from: Li+, Na+, K+, Ca++, Mg++, tetralkylammonium, tetralkylphosphonium, with a compound of formula (C), as reported in the description, wherein R1-R12 and m, n, o, p, q, r, s are as defined above and Y is a suitable leaving group.

(NP 0004)

TITLE OF THE INVENTION

"PROCESS FOR PREPARING NITROOXYALKYL SUBSTITUTED ESTERS OF CARBOXYLIC ACIDS, INTERMEDIATES USEFUL IN SAID PROCESS AND PREPARATION THEREOF"

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The present invention relates to a process for preparing nitrooxyalkyl substituted esters of carboxylic acids, to intermediates useful in said process and to their preparation.

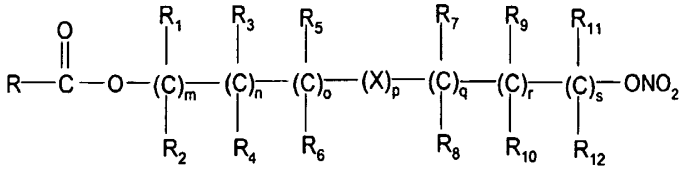
Many carboxylic acid nitrooxyalkyl esters are pharmacologically active products. For example, 1,4-dihydropyridine derivatives having nitrooxy moieties at the C-3 and/or C-5 ester position have shown to be active calcium-channel blockers similar to nifedipine and nicardipine (J. Chem. Soc. Perkin Trans I, 525 (1993)). In literature, several methods for synthesizing nitrooxyalkyl esters are reported. In this way, the nitrooxy moiety may be for example introduced by nucleophilic substitution of a leaving group already present on the alkyl chain of alkyl ester precursor. In particular, 2-(6-methoxy-2-naphtyl)-propionic acid 4-nitrooxybutyl ester has been synthesized reacting 4-chlorobutyl 2-(6-methoxy-2-naphtyl)-propionate with silver nitrate (WO 95/09831), whereas 2-(benzoylphenyl)propionic acid 4-nitrooxybutyl ester (ketoprofen nitrooxybutyl ester) has been prepared reacting the 2-(3-benzoylphenyl)propionic acid sodium salt with 1,4-dibromobutane to give the corresponding bromobutyl ester, which was then treated with silver nitrate to yield the desired nitrooxy derivative. Both processes have the disadvantage that during the introduction of nitrooxy group, impurities of difficult removal are often obtained, such as silver salts (AgCl,

AgBr) and silver metal, this being prejudicial to the use of the end-products in therapeutic field, in which an improved purity is always requested.

A further known process for preparing the above mentioned nitrooxyalkyl esters is the insertion of nitrooxyalkyl group by reacting the carboxylic acid or a derivative thereof (halide) with a nitrooxyalkyl alcohol or with a nitrooxyalkyl bromide. For example, 2-(S)-(6-methoxy-2-naphtyl)-propionic acid 4-nitrooxybutyl ester is prepared treating the corresponding acid chloride with 4-nitrooxybutan-1-ol in methylene chloride and in presence of potassium carbonate (WO 01/10814). This method has also the disadvantage that several by-products are formed, being in fact very difficult to obtain nitrooxyalkyl alcohols and the acyl halide in a pure form; moreover, for example 4-nitrooxybutan-1-ol is stable only in solution and it cannot be isolated as a pure substance.

It was thus an object of the present invention to provide a new process for preparing carboxylic acid nitrooxyalkyl esters not having the above mentioned disadvantages and wherein impurities and by-products are present in an essentially negligible amount.

The present invention relates to a process for preparing a compound of general formula (A)



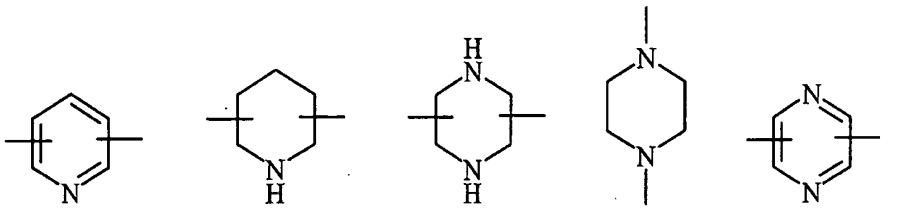
(A)

wherein R_1-R_{12} are the same or different and independently are hydrogen, straight or branched C_1-C_6 alkyl, optionally substituted with aryl;

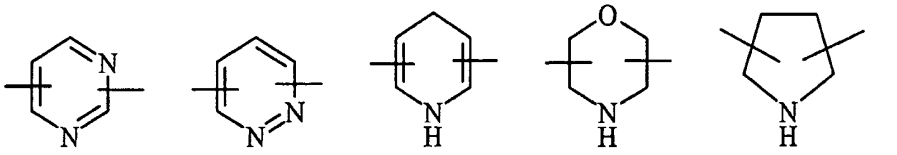
m, n, o, q, r and s are each independently an integer from 0 to 6, and p is 0 or 1, and

X is O, S, SO, SO_2, NR_{13} or PR_{13}, in which R_{13} is hydrogen, C_1-C_6 alkyl, or X is selected from the group consisting of:

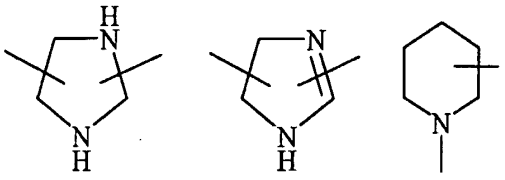
- saturated or unsaturated C_5-C_7 cycloalkylene, optionally substituted with one or more straight or branched C_1-C_3 alkyl groups;
- arylene, optionally substituted with one or more halogen atoms, straight or branched alkyl groups containing from 1 to 4 carbon atoms, or a straight or branched C_1-C_3 perfluoroalkyl;
- a 5 or 6 member saturated, unsaturated, or aromatic heterocyclic ring selected from



(X1) (X2) (X3) (X4) (X5)



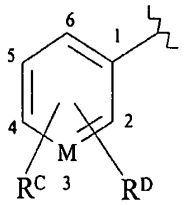
(X6) (X7) (X8) (X9) (X10)



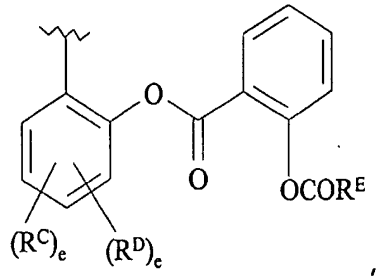
(X11) (X12) (X13)

wherein the bonds, when they have an undefined position, are intended to be in any possible position in the ring;

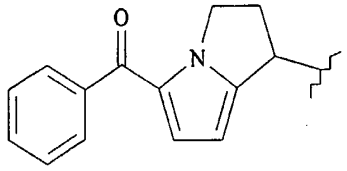
R is selected from:



(I)



(II)



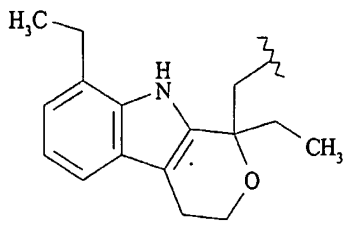
(III)

wherein M is a carbon or nitrogen atom;

R^C is selected from: H, OH, NH_2, R^ECONH-, R^ECOO-, an heterocyclic residue with 5 or 6 atoms that may be aromatic, saturated or unsaturated, containing one or more heteroatoms selected from oxygen, nitrogen or sulfur, and phenylamino (PhNH-), in which the aromatic ring may be substituted with one or more substituents selected from the group consisting of halogen, preferably chlorine or fluorine, straight or branched C_1-C_4-alkyl, for example methyl, straight or if possible branched perfluoroalkyl, for example trifluoromethyl;

R^E is selected from the group consisting of straight or branched C_1-C_5-alkyl, phenyl substituted with $OCOR^F$, wherein R^F is selected from the group consisting of methyl, ethyl or straight or branched C_3-C_6-alkyl or phenyl;

R^D is selected from: H, OH, halogen, -NH_2, straight or branched C_1-C_6-alkoxy, perfluoroalkyl having from 1 to 4 carbon atoms, for example -CF_3, mono o di-(C_1-C_6)alkylamino; with the proviso that R^C and R^D can not be both H;



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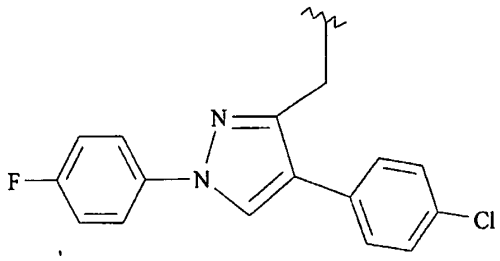

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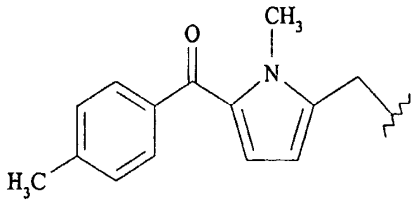

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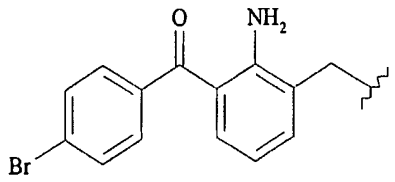

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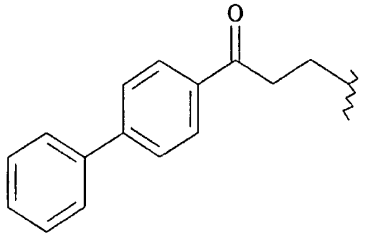

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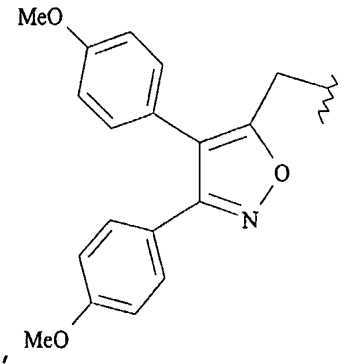

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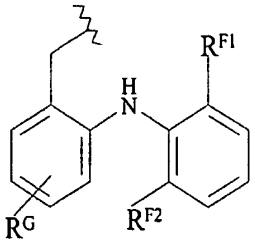
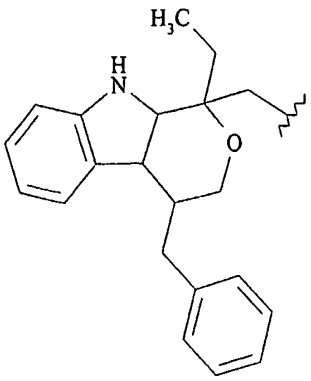


(X)

wherein R^{F1} and R^{F2} are halogens selected from chlorine, fluorine or bromine, R^G is hydrogen, straight or branched C_1-C_6-alkyl, preferably methyl;



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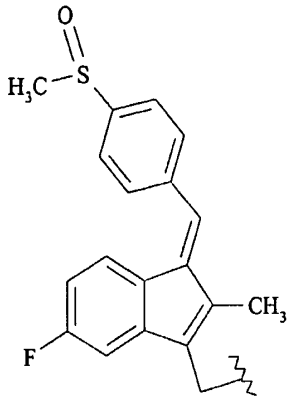

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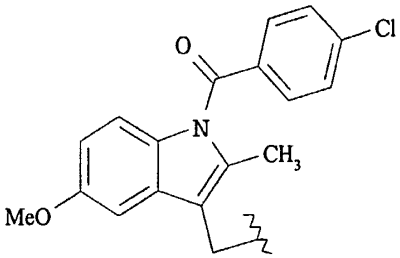

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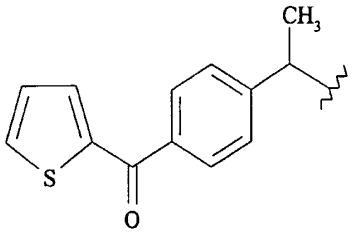

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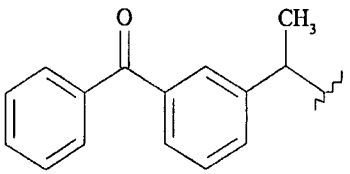

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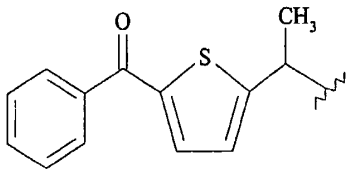

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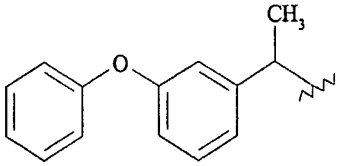

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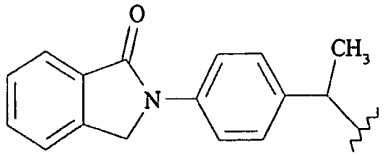

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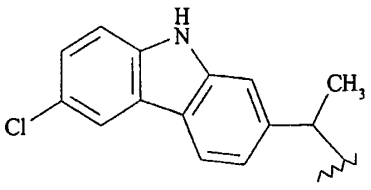

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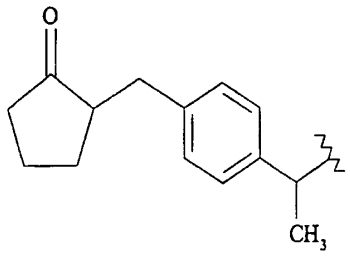
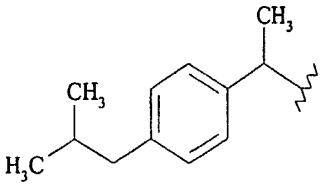


(XXI)



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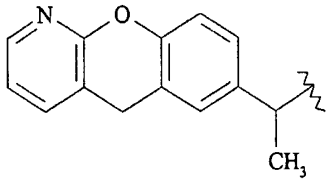

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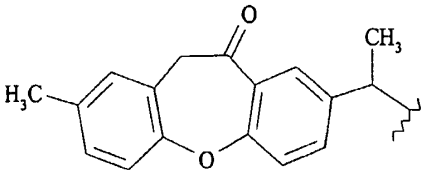

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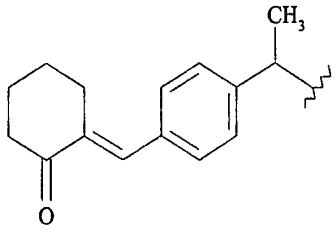

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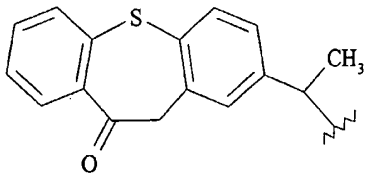

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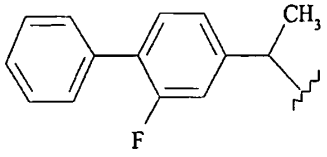

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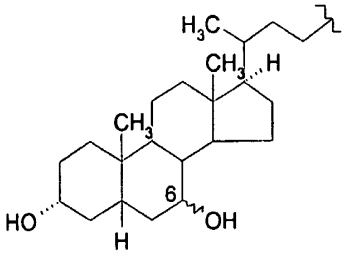
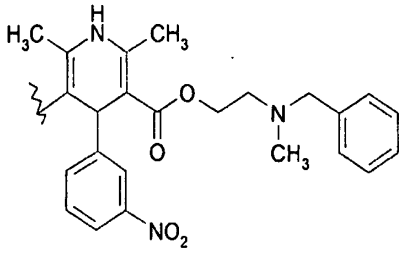


(XXVIII)

wherein the bond at 6 position in formula (XXVIII) may be α or β;



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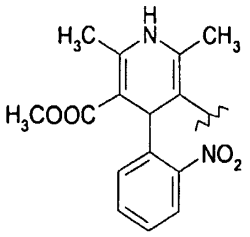

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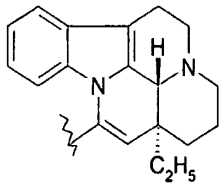
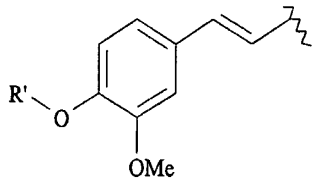


(XXXI)



(XXXII)

wherein R' in formula (XXXII) is H or R(CO)-, in which R is selected from the radicals represented by formulae (I)-(XXXI);

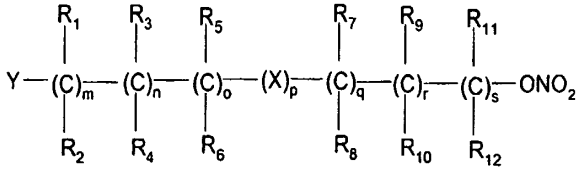
in all the formulae (I-XXXII) listed above, the wavy line represents always the position wherein -COO- group is bound;

said process comprising reacting a compound of formula (B)

R-COOZ (B)

wherein R is as above defined and Z is hydrogen or a cation selected from: Li+, Na+, K+, Ca++, Mg++, trialkylammonium tetralkylammonium, tetralkylphosphonium,

with a compound of the following formula (C)



(C)

wherein R_1-R_{12} and m,n,o,p,q,r,s are as defined above and Y is selected from

- an halogen atom such as Br, Cl, I;

- $-BF_4$, $-SbF_6$, FSO_3-, R_ASO_3-, in which R_A is a straight or branched C_1-C_6 alkyl, optionally substituted with one or more halogen atoms, or a C1-C6 alkylaryl;
- R_BCOO^-, wherein R_B is straight or branched C_1-C_6 alkyl, aryl, optionally substituted with one or more halogen atoms or NO_2 groups, C_4-C_{10} heteroaryl and containing one or more heteroatoms, which are the same or different, selected from nitrogen, oxygen sulfur or phosphorus;
- aryloxy optionally substituted with one or more halogen atoms or NO_2 groups, or heteroaryloxy.

In particular when in formula (A) the R residue is as defined by formula (I), wherein M is a carbon atom, R^C = R^ECOO- in 2 position, in which R^E is CH_3 and R^D = H, the compound is known as acetylsalicylic acid;

when in formula (A) the R residue is represented by formula (I), wherein M is a carbon atom, R^C = NH_2 in 5 position, R^D = OH in 2 position, the compound is known as mesalamine;

when in formula (A) the R residue is represented by formula (I), in which M is a carbon atom, R^C = PhNH- in 2 position, wherein Ph- is the 3-trifluoromethylbenzene radical, R^D = H, the compound is known as flufenamic acid;

when in formula (A) the R residue is represented by formula (I), in which M is a carbon atom, R^C = PhNH- in 2 position, wherein Ph is the 2,6-dichloro-3-methyl-benzene moiety, and R^D = H, the compound is known as meclofenamic acid;

when in formula (A) the R residue is represented by formula (I), in which M is a carbon atom, R^C = PhNH- in 2 position, wherein Ph è the 2,3-dimethylbenzene radical, and R^D = H, the compound is known as mefenamic acid;

when in formula (A) the R residue is defined by formula (I), in which M is a carbon atom, R^C = PhNH- in 2 position, wherein Ph is a 2-methyl-3-chlorobenzene group, and R^D = H, the compound is known as tolfenamic acid;

when in formula (A) the R residue is represented by formula (I), in which M is a nitrogen atom, R^C = PhNH- in 2 position, wherein Ph is the 2-trifluoromethylbenzene radical, and R^D = H, the compound is known as niflumic acid;

when in formula (A) the R residue is represented by formula (I), in which M is a nitrogen atom, R^C = PhNH- in 2 position, wherein Ph is the 2-methyl-3-trifluoromethylbenzene radical, and R^D = H, the compound is known as flunixin;

when in formula (A) the R residue is represented by formula (II), in which e = 0 and R^E is a methyl group, the compound is known as acetylsalicylsalicylic acid;

when in formula (A) the R residue is defined by formula (III), the compound is known as Ketorolac;

when in formula (A) the R residue is represented by formula (IV), the compound is known as etodolac;

when in formula (A) the R residue is represented by formula (V), the compound is known as pirazolac;

when in formula (A) the R residue is defined by formula (VI), the compound is known as tolmetin;

when in formula (A) the R residue is defined by formula (VII), the compound is known as bromfenac;

when in formula (A) the R residue is represented by formula (VIII), the compound is known as fenbufen;

when in formula (A) the R residue is represented by formula (IX), the compound is known as è mofezolac;

when in formula (A) the R residue is represented by formula (X), wherein R^{F1} and R^{F2} are Cl and R^G is hydrogen, the compound is known as diclofenac;

when in formula (A) the R residue is defined by formula (X), wherein R^{F2} is chlorine, R^{F1} is fluorine and R^G is a methyl group, the compound is known as COX-189;

when in formula (A) the R residue is represented by formula (XI), the compound is known as pemedolac;

when in formula (A) the R residue is defined by formula (XII), the compound is known as sulindac;

when in formula (A) the R residue is defined by formula (XIII), the compound is known as indomethacin;

when in formula (A) the R residue is represented by formula (XIV), the compound is known as suprofen;

when in formula (A) the R residue is represented by formula (XV), the compound is known as ketoprofen;

when in formula (A) the R residue is represented by formula (XVI), the compound is known as tiaprofenic acid;

when in formula (A) the R residue is defined by formula (XVII), the compound is known as fenoprofen;

when in formula (A) the R residue is defined by formula (XVIII), the compound is known as indoprofen;

when in formula (A) the R residue is represented by formula (XIX), the compound is known as carprofen;

when in formula (A) the R residue is defined by formula (XXI), the compound is known as loxoprofen;

when in formula (A) the R residue is represented by formula (XXII), the compound is known as ibuprofen;

when in formula (A) the R residue is defined by formula (XXIII), the compound is known as pranoprefen;

when in formula (A) the R residue is defined by formula (XXIV), the compound is known as bermoprofen;

when in formula (A) the R residue is represented by formula (XXV), the compound is known as CS-670;

when in formula (A) the R residue is defined by formula (XXVI), the compound is known as zaltoprofen;

when in formula (A) the R residue is represented by formula (XXVII), the compound is known as flurbiprofen;

when in formula (A) the R residue is represented by formula (XXVIII), in which bond to the hydroxy group at 6 position is β standing, the compound is known as ursodeoxycholic acid;

when in formula (A) the R residue is represented by formula (XXVIII), wherein bond to the hydroxy group at 6 position is α standing, the compound is known as chenodeoxycholic acid;

when in formula (A) the R residue is represented by è formulae (XXIX) and (XXX), the compounds belong to the nifedipine class;

when in formula (A) the R residue is defined by formula (XXXI), the compound is known as apovincaminic acid;

when in formula (A) the R residue is represented by formula (XXXII), wherein R' is hydrogen, the compound is known as ferulic acid;

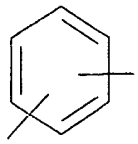
It has been surprisingly found that when in the compound of formula (B) R is the radical of formula (XXXII) wherein R' is H (ferulic acid) the reaction is highly selective towards the formation of the ester of formula (A), in spite of the fact that the presence of two nucleophilic groups in the ferulic acid (the carboxylic group and the fenolic group) could give a substantial formation of the nitroxyalkylether.

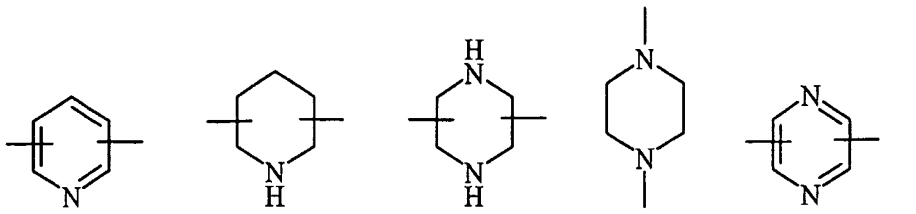
Preferably the present invention relates to a process for preparing a compound of formula (A) as above defined wherein:

the substituents R_1-R_{12} are the same or different and independently are hydrogen or straight or branched C_1-C_3 alkyl,

m, n, o, p, q, r and s are as defined above,

X is O, S or





(X1) (X2) (X3) (X4) (X5)

Most preferably the present invention relates to a process for preparing a compound of formula (A) as above defined wherein R_1-R_4 and R_7-R_{10} are hydrogens, m, n, q, r, are 1, o and s are 0, p is 0 or 1, and X is O or S.

Preferred compounds of formula (C) as above defined are those wherein Y is selected from the group consisting of -BF_4, -SbF_6, FSO_3-, CF_3SO_3-, $C_2F_5SO_3$-, $C_3F_7SO_3$-, $C_4F_9SO_3$-, p-$CH_3C_6H_4SO_3$-.

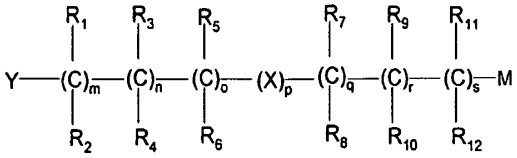
The reaction is carried out in an organic solvent, generally an aprotic, dipolar solvent such as acetone, tetrahyrofurane, dimethylformamide, N-methylpyrrolidone, sulfolane, acetonitrile.

Alternatively the above reported reaction is carried out in a biphasic system comprising an organic solvent selected from toluene, chlorobenzene, nitrobenzene, tert-butyl-methylether and a water solution wherein the organic solution contains (C) and the water solution contain an alkaline metal salt of (B), in presence of a phase transfer catalyst such as onium salts, for example tetralkylammonium and tetraalkylphosphonium salts.

The compounds of formula (B) and (C) are reacted at a (B)/(C) molar ratio of 2-0.5, preferably of 1.5-0.7 and at a temperature ranging from 0°C to 100°C, preferably from 15°C to 80°C.

The carboxylic acid salt may be prepared separately or may be generated "*in situ*", for example performing the reaction between (B) and (C) in the presence of a stoichiometric amount of a tertiary amine, or employing an amount in excess of said amine.

Another object of the present invention is the preparation of compounds of formula (C), by nitrating compounds of formula (D) reported here below, with a nitrating agent such as sulfonitric mixture and the like:

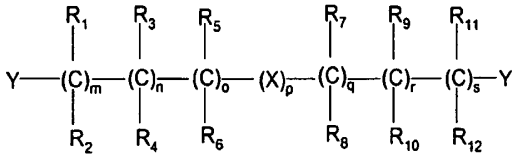


(D)

wherein M is OH, and

Y, X, m, n, o, p, q, r, s and R_1-R_{12}, have the meanings mentioned above.

Further object of the present invention is the preparation of compounds of formula (C), characterized in that a compound of the following formula (E) is reacted with nitrating agents selected for example from alkaline metal nitrates, quaternary ammonium nitrates, quaternary phosphonium salts and $AgNO_3$, $Zn(NO_3)_2$ $6H_2O$:

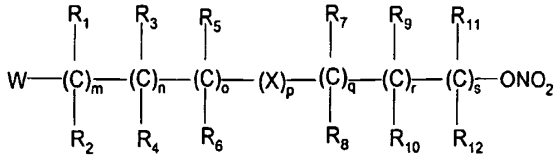


(E)

wherein:

Y, X, m, n, o, p, q, r, s and R_1-R_{12}, have the meanings mentioned above.,

Another object of the present invention is the preparation of compounds of formula (C), characterized in that a compound of formula (F)



(F)

wherein W is OH or halogen is reacted with a compound selected from alkanoylsulfonylchloride, trifluoromethansulfonic acid anhydride when W is OH or $AgSbF_6$, $AgBF_4$, $AgClO_4$, CF_3SO_3Ag, $AgSO_3CH_3$, $CH_3C_6H_4SO_3Ag$ when W is halogen.

Nitration of compound (D) was performed in an organic solvent, generally in a solvent selected from acetone, tetrahydrofurane, dimethylformamide, N-methylpyrrolidone, sulfolane, acetonitrile, methylene chloride etc., with nitrating agents selected from transition metal salts or, when M is OH, with nitrating systems based on nitric acid, such as the sulfonitric mixture.

The (D)/nitrating agent molar ratio is of from 2 to 0.5, in particular of 1.5 to 0.5.

Nitration was performed at a temperature ranging from 0°C to 100°C, preferably from 15°C to 80°C.

The reaction product (C) may be isolated or its solution can be employed as such for the reaction with substrate (B) to give (A).

Nitration of compound (E) was carried out in an organic solvent, generally in a solvent selected from acetone, tetrahydrofurane, dimethylformamide, N-methylpyrrolidone, sulfolane, acetonitrile, methylene chloride etc., with nucleophilic nitrating agents such as alkaline metal nitrates, onium salt nitrates, for example

tetraalkylammonium, tetraalkyl-phosphonium or trialkylammonium nitrate and so on.

Nitration was performed at a temperature of from 0°C to 100°C, in particular of 15°C to 80°C.

The molar ratio between (E) and the nitrating agent is of from 20 to 2, preferably of 8 to 1.

The reaction product (C) may be isolated or its solution can be employed such as in the reaction with substrate (B) to give (A).

The reaction for obtaining compound (C) from (F) was carried out in an organic solvent, generally selected from the group consisting of acetone, tetrahydrofurane, dimethylformamide, N-methylpyrrolidone, sulfolane, acetonitrile, methylene chloride and the like, with a reactive compound selected from transition metal salts of Y or, when W is OH, the reaction was performed with an acid chloride such as methanesulfonyl chloride etc., or with a suitable anhydride such as trifluoro-methanesulfonic anhydride.

The reaction was performed at a temperature ranging from -20°C to 100°C, in particular from -20° to 60°C.

The molar ratio between (F) and the reagent is of from 2 to 0.5, preferably of 1.5 to 0.5.

The reaction product (C) may be isolated or its solution can be employed as such in the reaction with substrate (B) to give (A).

The following examples are to further illustrate the invention without limiting it.

EXAMPLES

Preparation of 4-nitrooxybutyl bromide according to Chem. Pharm. Bull.,1993,41,1040

Nitric acid (90%, 0.8 mol) was dropped under stirring in sulfuric acid maintained at 0°C (0.8 mol) and the mixture was then stirred at 0°C for 80 minutes. In the solution thus obtained and maintained at 0°C, under stirring 4-bromobutanol was dropped (0.4 mol) and the mixture was stirred at the same temperature for additional 210 minutes. The solution was then poured in a water-ice mixture and extracted twice with diethyl ether. The ether extracts were combined together and washed with a sodium bicarbonate saturated solution. The solvent was evaporated off under vacuum to give a yellow oil (yield: 84.8%).

Example 1

Preparation of 4-nitrooxybutyl p-toluenesulfonate

To a solution of 4-bromobutanol (5.0 g, 33 mmol) in pyridine (50 ml) kept at 0°C, under stirring and under nitrogen atmosphere tosyl chloride (6.8 g, 36 mmol) was added. The resulting solution was kept under stirring for further 20 minutes and then stored overnight at -18°C. The reaction mixture was poured in a water/ice mixture (about 400 ml) and extracted with ethyl ether (500 ml). The organic phase was washed with 6N hydrochloric acid (500 ml) and dried on sodium sulfate. After evaporation of the solvent under vacuum, an oily residue was obtained (7 g). To a solution of the oily residue (7 g) in acetonitrile (50 ml) and maintained under stirring at room temperature, silver nitrate (7.8 g, 46 mmol) was added. After nearly 15 minutes, the formation of a yellow, insoluble product was observed. The heterogeneous mixture was kept under stirring overnight. The insoluble was removed by filtration and the solution was poured in water (200 ml) and extracted with ethyl ether (2x250ml). The combined organic extracts were

dried over sodium sulfate. Evaporation of the solvent under vacuum afforded an oily residue (5 g).

Chromatography of the residue on silica gel (100 g), by hexane/ethyl ether mixture as eluent, gave the title product (3 g), m.p. 38-40°C, purity higher than 98%, determined by HPLC.

FTIR (solid KBr, cm -1): 2966, 1626, 1355, 1281, 1177,1097, 959, 876, 815, 663, 553.

300 MHz 1H NMR (CDCl3) delta 1,77 (m, 4H); 2,35 (s, 3H); 4,06 (m, 2H); 4,38 (m, 2H); 7,36 (2H); 7,7 (2H).

Example 2A

Sinthesis of (E)-3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid 4-nitrooxybutyl ester

A mixture obtained pouring ferulic acid (1.94 g, 10 mmol), 4-nitrooxybutyl bromide (1.98 g, 10 mmol) and triethylamine (1.21 g, 12 mmol) in dimethylformamide (10 ml), was stirred for 3 days at 25°C. After evaporation in vacuo of DMF, an oil was obtained (2.3 g) that, according to NMR and HPLC analysis, mainly consists of unreacted ferulic acid and its 4-nitrooxybutyl ester. The ester was separated from acid by flash chromatography with a 65% yield.

Example 2B

Synthesis of (E)-3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid 4-nitrooxybutyl ester

(E)-3-(4-Hydroxy-3-methoxyphenyl)-2-propenoic acid (670 mg, 3.46 mmol) and 4-(nitrooxy)butyl 4-p-toluensulfonate (1.00 g, 3.46 mmol) were dissolved in 40 ml of DMF and the solution poured in a three-necked flask kept under argon and under magnetic stirrer. Subsequently, triethylamine (0.52 ml, 3.81 mmol) was added and the mixture was allowed

to react at room temperature. The course of the reaction was followed by TLC (EtOAc as the eluent) and by LC/MS ESI- using a RP-C18 4.6x100 mm column. After 72 hours the reaction conversion was ca. 40%. Additional 0.1 equivalents of tosylate were then added to the solution (100 mg, 0.346 mmol) and the mixture was reacted for other 24 hours. After this period the solution was poured in water and extracted with Et_2O (3 x 75 ml). The combined organic phases were washed with a saturated solution of $NaHCO_3$ and water, dried over Na_2SO_4 and concentrated under reduced pressure.
The residue was chromatographed over silica gel (using ethyl acetate / petroleum ether 9 : 1 as the eluent) to provide the desired ester product in 70% yield.
The IR and LC-MS ESI- spectra of the peak product were identical to those of an authentic sample.

Analyses

TLC: (Ethyl acetate) Rf=0.60

HPLC purity: 72 %

MS (ESI neg): 310 (M - H)

IR(film) cm^{-1}: 3450 (br OH), 2964, 1707 (C=O), 1631(ONO_2), 1599, 1514, 1448, 1280 (ONO_2).

Example 3A

Synthesis of 5-t-butoxycarbonylamino-2-hydroxyben-zoic acid 4-(nitrooxy)butyl ester

The process of Example 2A was repeated, replacing however ferulic acid by 5-t-butoxycarbonylaminosalicilic acid. The title compound was obtained with a yield of 50%.

Example 3B

Synthesis of 5-t-butoxycarbonylamino-2-hydroxybenzoic acid 4-(nitrooxy)butyl ester

To a mixture comprising DMF (200 ml), 5-t-butoxycarbonylaminosalicylic acid (4.37 g, 17.3 mmol) and 4-nitrooxybutyl p-toluenesulfonate (5 g, 17.3 mmol), at room temperature and under stirring triethylamine was added (2,6 ml; 19 mmol). The reaction mixture was maintained 3 days under stirring at room temperature. It was then poured in water and extracted with ethyl ether. The combined organic phases were washed with a sodium carbonate solution and then with water. After drying on sodium sulfate, the evaporation of the solvent yields a raw product that purified by silica gel chromatography gives the title compounds with a yield of 65%.

Example 4

Synthesis of potassium (E)-3-(4-hydroxy-3-methoxyphenyl)-2-propenoate

Potassium hydroxide (580 mg, 10.3 mmol) was dissolved in methanol (10 ml) and put in a three-necked flask. Stirring was set on. Subsequently, (E)-3-(4-Hydroxy-3-methoxyphenyl)-2-propenoic acid (2.00 g, 10.3 mmol) in methanol (20 mL) was added to this solution through a funnel. After the addition was ended, the solution was allowed to react at room temperature for 3 h. Methanol was then evaporated off and then yellow solid residue was washed with Et_2O and dried under reduced pressure.

The product was obtained as a yellowish solid (2.40 g, quantitative yield).

Analyses

IR(KBr) cm^{-1}: 3388, 1643, 1561 (C=O), 1524, 1404, 1263, 1204, 1152, 1121.

Example 5A

Synthesis of (E)-3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid 4-(nitrooxy)butyl ester

Potassium (E)-3-(4-Hydroxy-3-methoxyphenyl)-2-propenoate (1.00 g, 4.3 mmol) was dissolved in 40 ml of DMF and poured in a three-necked flask kept under argon and magnetic stirring. The mixture was cooled at 0-5 °C through an ice bath and 4-(nitrooxy)butyl 4-p-toluensulfonate (1.25 g, 4.3 mmol) in DMF (10 ml) was added through a funnel. After the addition, the resulting mixture was stirred under argon, while the temperature was allowed to rise to r.t. (25 °C). The reaction course was followed by TLC and LC/MS ESI-. After 6 hours the conversion was complete. The solution was then poured in water and extracted with Et_2O (3 x 75 ml). The combined organic phases were washed with a saturated solution of $NaHCO_3$ and water, dried over Na_2SO_4 and the volatiles removed under reduced pressure to provide a residue. The residue was washed with petroleum ether and dried under reduced pressure to provide the desire ester in 95% yield.

Analyses

HPLC purity: 95 % MS (ESI neg): 310 (M - H)

IR(film) cm^{-1}: 3450 (br OH), 2964, 1707 (C=O), 1631(ONO_2), 1599, 1514, 1448, 1280 (ONO_2).

^1H NMR ($CDCl_3$, 300 MHz): □ 1.72-1.93 (4H, m, CH_2-CH_2), 3.92 (3H, s, OCH_3), 4.22-4.26 (2H, m, CH_2-COO), 4.50-4.54 (2H, m, CH_2-ONO_2), 5.95 (1H, br s, OH), 6.28 (1H, d, J = 15.9Hz, CH=), 7.03-7.10 (2H, m, aromatic H), 7.36 (1H, d, J = 7.8 Hz, aromatic H), 7.61 (1H, d, J = 15.9Hz, CH=).

Example 5B

Synthesis of (E)-3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid 4-(nitrooxy)butyl ester

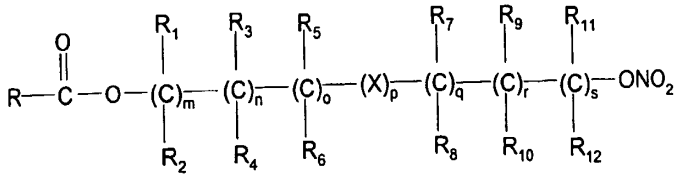
Ferulic acid (97 g, 0.50mol) was dissolved in methanol (750 ml) and mixed with a solution of potassium hydroxyde (33 g, 0.050 mol) in methanol (250 ml) to give a clear solution at 27°C. The potassium salt of ferulic acid was precipitated by addition of toluene (1250 ml).

The suspension was cooled to 20°C, filtered , and washed with toluene (250 ml) and pentane (2x250 ml). The wet cake was dissolved in DMF (750 ml), and potassium iodide (25 g) and crude 4-Bromo-1-butylnitrate (165 g, 0.83 mol) were added. The reaction mixture was stirred for 16 hours at 20-22°C. The reaction was added with water (750 ml) and the resulting mixture was extracted with t-Butyl-methylether (800 ml + 500 ml). The combined extracts were washed with water (750 ml), with 25% sodium chloride aqueous solution (250 ml), dried over sodium sulphate (250 g), filtered, and evaporated at 50°C (external bath water temperature) under vacuum to give a light brown oil (220 g). Cyclohexane (500 ml) was added, and the mixture was heated to 50°C to give a two phases system, a colorless upper phase and a dark lower phase. The stirred mixture was cooled to room temperature for 15 hours to give a dark solid cake and a white suspension of fluffy material. The solid was crushed and the suspension was filtered. The cake was washed with cyclohexane (2x50 ml) and dried at 45°C to provide the desired ester (128.8 g) with 92% purity.

Analytically pure product was obtained by crystallization from toluene.

CLAIMS

1. A process for preparing a compound of general formula (A)



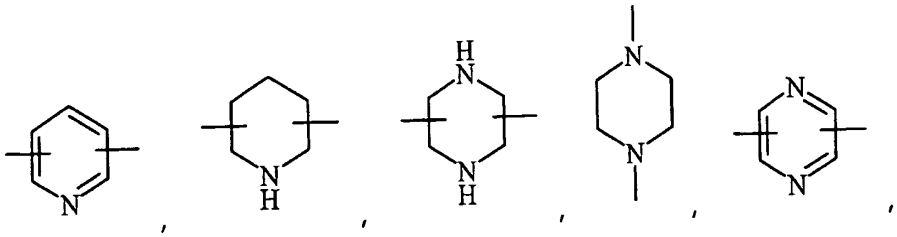
(A)

wherein R_1-R_{12} are the same or different and independently are hydrogen, straight or branched C_1-C_6 alkyl, optionally substituted with aryl;

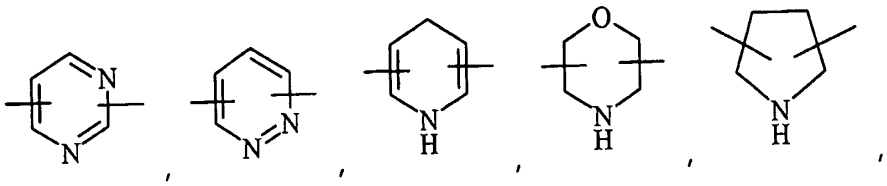
m, n, o, q, r and s are each independently an integer from 0 to 6, and p is 0 or 1, and

X is O, S, SO, SO_2, NR_{13} or PR_{13}, in which R_{13} is hydrogen, C_1-C_6 alkyl, or X is selected from the group consisting of:

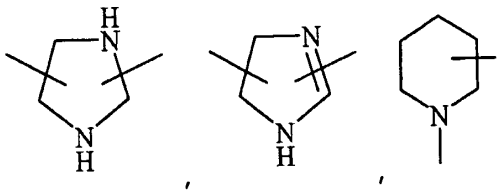
- saturated or unsaturated C_5-C_7 cycloalkylene, optionally substituted with one or more straight or branched C_1-C_3 alkyl groups;
- arylene, optionally substituted with one or more halogen atoms, straight or branched alkyl groups containing from 1 to 4 carbon atoms, or a straight or branched C_1-C_3 perfluoroalkyl;
- a 5 or 6 member saturated, unsaturated, or aromatic heterocyclic ring selected from



(X1) (X2) (X3) (X4) (X5)



(X6) (X7) (X8) (X9) (X10)



(X11) (X12) (X13)

and R is the radical of a pharmacologically active compound selected from the formulae (I)-(XXXI) listed in the specification or the ferulic acid radical of formula (XXXII), wherein R' is H, or a group R(CO)-, in which R is as above defined,

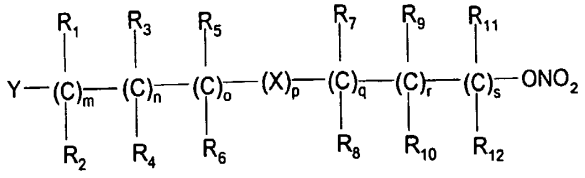
said process comprising reacting a compound of formula (B)

R-COOZ (B)

wherein R is as above defined and Z is hydrogen or a cation selected from

Li+, Na+, K+, Ca++, Mg++, tetralkylammonium, tetralkylphosphonium,

with a compound of formula (C)



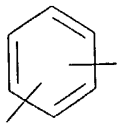
(C)

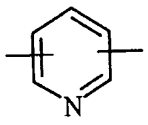
wherein R_1-R_{12} and m,n,o,p,q,r,s are as defined above and Y is selected from

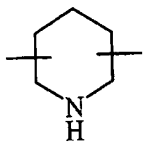
- a Br, Cl, I;
- $-BF_4$, $-SbF_6$, FSO_3-, R_ASO_3-, in which R_A is a straight or branched C_1-C_6 alkyl, optionally substituted with one or more halogen atoms, or a C1-C6 alkylaryl;

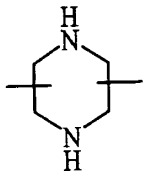
- R_BCOO^-, wherein R_B is straight or branched C_1-C_6 alkyl, aryl, optionally substituted with one or more halogen atoms or NO_2 groups, C_4-C_{10} heteroaryl and containing one or more heteroatoms, which are the same or different, selected from nitrogen, oxygen sulfur or phosphorus;
- aryloxy optionally substituted with one or more halogen atoms or NO_2 groups, or heteroaryloxy.

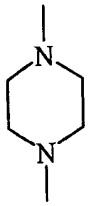
2. A process for preparing a compound of formula A according to claim 1 wherein:
the substituents R_1-R_{12} are the same or different and independently are hydrogen or straight or branched C_1-C_3 alkyl,
m, n, o, p, q, r and s are as defined above,
X is O, S or

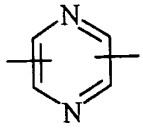



(X1)


(X2)


(X3)


(X4)


(X5)

3. A process for preparing a compound of formula A according to claim 1 or 2 wherein R_1-R_4 and R_7-R_{10} are hydrogens, m, n, q, r, are 1, o and s are 0, p is 0 or 1, and X is O or S.

4. A process for preparing a compound of formula A according to anyone of the preceding claims wherein R is the the ferulic acid radical of formula (XXXII)as reported

in the specification, wherein R'is H, or a group R(CO)-, in which R is the radical of a pharmacologically active compound selected from the formulae (I)-(XXXI) listed in the specification.

5. A process for preparing a compound of formula A according to claim 4 wherein in the compound of formula (B) Y is Br.

6. A process for preparing a compound of formula A according to anyone of the preceding claims wherein Y is selected from the group consisting of Br, Cl, I,.-BF_4, -SbF_6, ClO_4-, FSO_3-, CF_3SO_3-, $C_2F_5SO_3$-, $C_3F_7SO_3$-, $C_4F_9SO_3$-, p-$CH_3C_6H_4SO_3$-.

7. A process for preparing a compound of formula A according to anyone of the preceding claims wherein the reaction is performed in an organic solvent selected from acetone, tetrahydrofurane, dimethylformamide, N-methylpyrrolidone, sulfolane and acetonitrile.

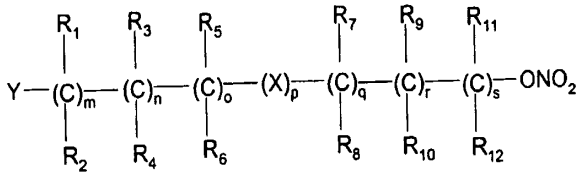
8. A process for preparing a compound of formula A according to anyone of the claims 1-4 wherein the reaction is performed in a biphasic system comprising an aprotic dipolar solvent selected from toluene, chlorobenzene, nitrobenzene, tert-butyl-methylether and a water solution wherein the organic solution contains (C) and the water solution contain an alkaline metal salt of (B), in presence of a phase transfer catalyst.

9. A process for preparing a compound of formula A according anyone of the preceding claims wherein the

reaction is performed at a temperature ranging from 0°C to 100°C.

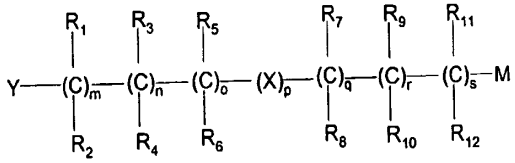
10. A process for preparing a compound of formula A according to anyone of the preceding claims wherein the compounds of formula B and C are reacted at a (B)/(C) molar ratio of 2-0.5.

11. A process for preparing a compound of formula (C)



(C)

wherein R_1-R_{12}, m, n, o, p, q, r, s, X, Y are as defined in claim 1-4, comprising reacting a compound of the following formula (D)



(D)

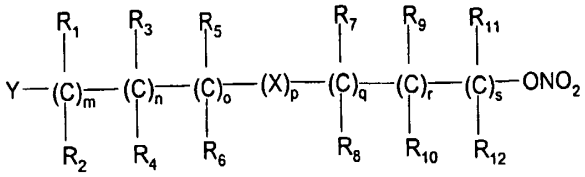
wherein M is OH and the other substituents and indices are as above defined, with a nitrating agent.

12. A process for preparing a compound of formula (C). according to claim 11 wherein the nitrating agent is sulfonitric mixture.

13. A process for preparing a compound of formula (C). according to claim 11-12 wherein the compound (D) and the nitrating agent are at molar ratio of 2-0.5.

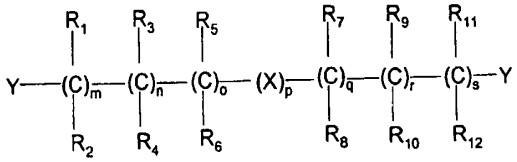
14. A process for preparing a compound of formula (C). according to claim 11-13 wherein the reaction is performed at a temperature ranging from 0°C to 100°C.

15. A process for preparing a compound of formula (C)



(C)

wherein R_1-R_{12}, m, n, o, p, q, r, s, X, Y are as defined in claim 1-4, comprising reacting a compound of the following formula (E),



(E)

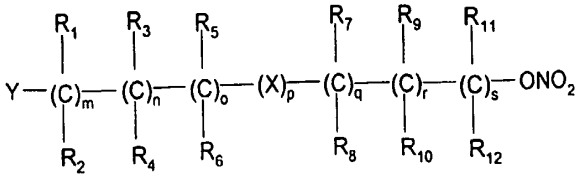
wherein R_1-R_{12}, m, n, o, p, q, r, s, X, Y are as defined above with a nitrating agent.

16. A process for preparing a compound of formula (C). according to claim 15 wherein the nitrating agent is selected from alkaline metal nitrates, quaternary ammonium nitrates, quaternary phosphonium nitrates, $AgNO_3$, $Zn(NO_3)_2$ $6H_2O$.

17. A process for preparing a compound of formula (C). according to claims 15-16 wherein the compound (E) and the nitrating agent are at molar ratio of 20:2.

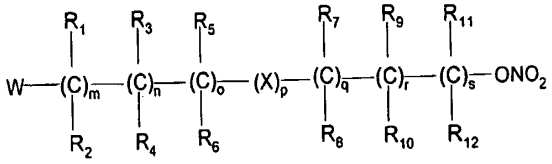
18. A process for preparing a compound of formula (C). according to claims 15-17 wherein the reaction is performed at a temperature ranging from 0°C to 100°C.

19. A process for preparing a compound of formula (C)



(C)

wherein R_1-R_{12}, m, n, o, p, q, r, s, X, Y are as defined in claim 1-4, comprising reacting a compound of the following formula (F),



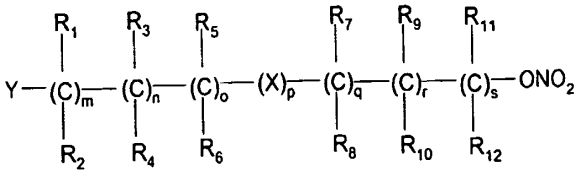
(F)

wherein R_1-R_{12}, m, n, o, p, q, r, s, X, are as defined above, W is OH or halogen, with a compound selected from alkanoylsulfonylchloride and trifluoromethansulfonic anhydride when W is OH or with $AgSbF_6$, $AgBF_4$, $AgClO_4$, CF_3SO_3Ag, $AgSO_3CH_3$, $CH_3C_6H_4SO_3Ag$ when W is halogen.

20. A process for preparing a compound of formula (C) according to claim 19 wherein the compound (F) and the nitrating agent are at molar ratio of 2:0.5.

21. A process for preparing a compound of formula (C). according to claims 19-20 wherein the reaction is performed at a temperature ranging from 0°C to 100°C.

22. A compound of formula (C)



(C)

wherein R_1-R_{12}, m, n, o, p, q, r, s, X, Y are as defined in claim 1-4 with the proviso that Y is not halogen.

23. Use of nitrooxyalkyl derivatives of general formula (C) according to claim 20 as intermediates for preparing carboxylic acid nitrooxyalkyl esters of formula (A) according to claim 1-4.

INTERNATIONAL SEARCH REPORT

Internati[illegible] Application No
PCT/EP 03/08700

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C203/04 C07C201/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal, WPI Data, BEILSTEIN Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; MOVSUMZADE, M. M. ET AL: "Effect of bromine nitrate on olefin-oxirane mixtures" retrieved from STN Database accession no. 84:73719 XP002262956 abstract & ZHURNAL ORGANICHESKOI KHIMII (1975), 11(12), 2508-10 , --- -/--	22

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 December 2003	14/01/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bedel, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internati[illegible] Application No
PCT/EP 03/08700

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; MCKILLOP, A. ET AL: "Mercury-assisted solvolyses of alkyl halides. Simple procedures for the preparation of nitrate esters, acetate esters, alcohols, and ethers" retrieved from STN Database accession no. 82:30915 XP002262957 abstract & TETRAHEDRON (1974), 30(15), 2467-75 ,	22
X	OGAWA T ET AL: "SYNTHESIS AND ANTIHYPERTENSIVE ACTIVITIES OF NEW 1,4-DIHYDROPYRIDINE DERIVATIVES CONTAINING NITROOXYALKYLESTER MOIETIES AT THE 3- AND 5-POSITIONS" CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO, JP, vol. 41, no. 6, June 1993 (1993-06), pages 1049-1054, XP001093850 ISSN: 0009-2363 page 1050 -page 1052; figures; tables	22
Y	see compound XII and method C	1-21,23
X	KAWASHIMA ET AL: "Synthesis and Pharmacological Evaluation of (Nitrooxy)alkyl Apovincaminates" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 36, 1993, pages 815-819, XP002210204 ISSN: 0022-2623 page 817, right-hand column, paragraph 4	22
Y	page 818, right-hand column, paragraph 2 -page 819, left-hand column, paragraph 3	1-21,23
X	WO 98 07701 A (PIATTI SUSANA ELIDA ;ALDOMA GUSTAVO ENRIQUE (AR); HANDFORTH INVEST) 26 February 1998 (1998-02-26) claim 1	22
Y	WO 95 30641 A (NICOX LTD ;DEL SOLDATO PIERO (IT); SANNICOLO FRANCESCO (IT)) 16 November 1995 (1995-11-16) claims; examples	1-21,23

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/08700

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1,2,22
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,2,22

Present claims 1,2 and 22 relate to an extremely large number of possible compounds and methods. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds and methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds and methods according to the substituant definitions of claim 3.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internatio[illegible] Application No
PCT/EP 03/08700

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9807701 A	26-02-1998	WO 9807701 A1	26-02-1998
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